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*Biochim Biophys Acta* 2002 Apr 29;1596(2):381-91

## **Inhibition of yeast lipase (CRL1) and cholesterol esterase (CRL3) by 6-chloro-2-pyrones: comparison with porcine cholesterol esterase.**

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Previously, it was demonstrated that pancreatic cholesterol esterase is selectively inhibited by 6-chloro-2-pyrones with cyclic aliphatic substituents in the 3-position. Inhibition is reversible and is competitive with substrate. Pancreatic cholesterol esterase is a potential target for treatment of hypercholesterolemia. In the present study, yeast cholesterol esterase from *Candida cylindracea* (also called C. rugosa CRL3) was compared to porcine pancreatic cholesterol esterase for inhibition by a series of 3-alkyl- or 5-alkyl-6-chloro-2-pyrones. In addition, CRL3 was compared with the related yeast lipase CRL1. Inhibition of CRL3 by substituted 6-chloro-2-pyrones was competitive with binding of the substrate p-nitrophenyl butyrate. Inhibition constants ranged from 0.2  $\mu\text{M}$  to  $>90 \mu\text{M}$ . Small changes in the alkyl group had profound effects on binding. The pattern of inhibition of CRL3 is quite distinct from that observed with porcine cholesterol esterase. Molecular modeling studies suggest that the orientation of binding of these inhibitors at the active site of CRL3 can vary but that the pyrone ring consistently occupies a position close to the active site serine. CRL1 is highly homologous to CRL3. Nevertheless, patterns of inhibition of CRL1 by substituted 6-chloro-2-pyrones differ markedly from patterns observed with CRL3. The substituted 6-chloro-2-pyrones are slowly hydrolyzed in the presence of CRL1 and are pseudosubstrates of CRL3, but are simple reversible inhibitors of pancreatic cholesterol esterase

PMID: 12007617, UI: 22003422

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